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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,376	07/10/2001	Thomas J. Brennan	R-599	8327

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DELTAGEN, INC.
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[REDACTED] EXAMINER

PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/903,376	BRENNAN, THOMAS J.
Examiner	Art Unit	
Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 28 May 2003.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) 1-7, 9, 11-16 and 24-27 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 8, 10 and 17-23 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 10 July 2001 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ .
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>6</u> .	6) <input type="checkbox"/> Other: _____ .

DETAILED ACTION

Claims 1-27 are pending.

Election/Restrictions

Applicant's election without traverse of Group III, claims 8, 10, and 17-23) in Paper No. 13 is acknowledged.

Claims 1-7, 9, 11-16, and 24-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. Any response to this Office Action, which fails to meet all of these requirements, will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

To avoid damage to a CRF by irradiation, a reply to a notice to comply with the sequence rules should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio (<http://www.uspto.gov/ebc/efs/downloads/documents.htm>), EFS Submission User Manual - ePAVE)
2. Mailed to: **U.S. Patent and Trademark Office, Box Sequence, P.O. Box 2327, Arlington, VA 22202**
3. Mailed by Federal Express, United Parcel Service or other delivery service to: **U. S. Patent and Trademark Office, 2011 South Clark Place, Customer Window, Box Sequence, Crystal Plaza Two, Lobby, Room 1B03, Arlington, Virginia 22202**
4. Hand Carried directly to the Customer Window at: **2011 South Clark Place, Crystal Plaza Two, Lobby, Room 1B03, Box Sequence, Arlington, Virginia 22202**

Drawings

The drawings filed on 7/10/01 are approved.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 10, and 17-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to making and using a transgenic non-human animal, particularly a mouse, comprising a disruption in the 5-HT-2B gene.

The specification teaches the generation of transgenic mice by disruption of the nucleotide sequence set forth in SEQ ID NO: 1, wherein SEQ ID NO: 1 encodes a 5-HT-2B. See pages 3-4 and the working example on pages 51-53, of the specification. The specification teaches that transgenic mice whose genomes comprise a homozygous disruption in a 5-HT-2B gene exhibit lethality between embryonic days 8.5 and 9.5, as a result of the disruption. See pages 51-53 of the specification. While discussing that embryos comprising a homozygous disruption of a 5-HT-3B gene die before birth the specification has not disclosed a particular phenotype exhibited by the embryos. The specification has also not disclosed a phenotype exhibited by a transgenic non-human animal comprising a heterozygous disruption of a 5-HT-2B gene. As the specification has not provided guidance that correlates to a phenotype resulting from disruption of a 5-HT-2B gene in a transgenic non-human animal, the specification has not taught how to use the transgenic non-human animals embraced by the claims. The working examples, guidance and relevant teachings provided by the instant specification are directed to the creation of the above transgenic mouse but do not support how to use such a mouse. See pages 51-53. Given the lack of guidance provided by the instant specification it would have required undue experimentation to use the transgenic non-human animals embraced by the claims.

The following aspect of the rejection under 35 U.S.C. 112, first paragraph is directed to claims 8, 10 and 17-23 as they read on transgenic knockout non-human animals, use of embryonic stem cells to make a transgenic mouse, and germline transmission of ES cells:

Both the specification and the state of the art have taught that the transgenic knockout technology requires the use of embryonic stem cells that have been genetically manipulated to comprise a disruption in a nucleotide sequence of interest. The specification has not taught creation of a transgenic knockout non-human animal by methods that do not require embryonic stem cells. Presently, the transgenic knockout technology is limited to the mouse system. See below.

With regard to the claim breadth directed to transgenic non-human animals, the specification fails to teach the production of any transgenic non-human animal comprising a disruption in a 5-HT-2B gene other than a transgenic knockout mouse. It is well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seemark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al (Journal of Clinical Investigation, 1996) state that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). Moreover, with regard to claims 10 and 22 neither the state of the art nor the prior art of record has provided guidance for use of cells, other than ES cells for production of a transgenic knockout mouse. It would be unpredictable if other cells could be used for the

production of a transgenic knockout mouse because other cells may be not totipotent or transmit through the germline as ES cells do. Even more, claims 8, 10 and 17-23 as written do not appear to require germline transmission of the disrupted nucleotide sequence. These claims may be broadly interpreted to read on a single cell comprising a disrupted nucleotide sequence. Since the claims do not require germline transmission of the disrupted nucleotide sequence it would be unpredictable if an ES cell comprises the disrupted nucleotide sequence. As stated above the evidence of record does not support germline transmission of non-ES cells. As the claims are directed to transgenic non-human animals (claim 8) or a method that requires the use of a cell to in the production of a transgenic mouse (claims 10 and 22), wherein the cell is interpreted to read on an embryonic stem cell (as in claims 10 and 22) comprising a disruption in a 5-HT-2B gene, which must be generated by the introduction of a transgene into an ES cell or transgenic non-human animals, particularly a mouse, that do not exhibit germline transmission of a disrupted nucleotide sequence, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice. Given the unpredictable state of the art it would have required undue experimentation for the skilled artisan to make and use the invention as claimed.

As a final issue the claims encompass transgenic non-human animals, particularly a mouse, that comprise a disruption in a 5-HT-2B gene that do not exhibit any particular phenotype specific resulting specifically from the disruption. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (Moreadith et al., 1997, J. Mol. Med., Vol. 75, pages 208-216; see

page 208, column 2, last full paragraph). Moens et al. (Development, Vol. 119, pages 485-499, 1993) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). The specification has asserted that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a 5-HT-2B. However, it would be difficult to predict any phenotype resulting from disruption of the sequence of SEQ ID NO: 1 in light of the above. The specification discloses that homozygous knockout mice comprising a disruption in the nucleotide sequence set forth in SEQ ID NO: 1 do not exist as the homozygous embryos die between days 8.5 and 9.5 during development and never develop to term. See pages 51-53 of the specification. The specification suggests that the homozygous knockout embryos exhibit embryonic lethality, abnormalities, retarded development, and are reabsorbed. Claim 17 however is directed to a transgenic mouse that exhibits embryonic lethality, abnormal embryos, retarded development, and reabsorbed embryos. It appears that the claims embrace a transgenic mouse that cannot exist as only the homozygous embryos die and are abnormal. Furthermore, such alleged phenotypes are overly broad and appear to be general, as abnormalities and retarded development appear to relate to any embryo that dies during development. In addition, the instant specification has not provided guidance that correlates to a phenotype resulting from a heterozygous disruption of a 5-HT-2B gene. As such it appears that a transgenic mouse comprising a heterozygous disruption of a 5-HT-2B gene does not exhibit a phenotype that differs from a wild-type mouse. Moreover, the skilled artisan would not know how to use a

transgenic knockout non-human animal that lacks a phenotype, particularly because the instant specification has not provided uses for such; the transgenic mice that have a phenotype may be used for drug testing or as models for diseases or disorders according to the instant specification. It is noted that claim 8 does not recite a phenotype resulting from disruption of a 5-HT-2B gene. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to use a transgenic non-human knockout animal that lacks a phenotype.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic non-human animals comprising a disruption in a 5-HT-2B gene, the lack of direction or guidance provided by the specification for the production of transgenic non-human animals comprising a disruption in a 5-HT-2B gene, the absence of working examples for the demonstration or correlation to the production of a transgenic knockout non-human animal that exhibits a phenotype, the unpredictable state of the art with respect to a phenotype that results from disruption of a given nucleotide sequence, the undeveloped art pertaining to the establishment of true embryonic stem (ES) cells of animal species other than mouse, and the breadth of the claims drawn to any phenotype associated with embryonic lethality, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.
Art Unit 1632

PETER PARAS
PATENT EXAMINER



**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING
NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- 7. Other: Fig. 2A contains an unidentified sequence.

Applicant Must Provide:

- An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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